



**HAL**  
open science

## Activation of STING in the pancreatic tumor microenvironment: a novel therapeutic opportunity

Hanane Chamma, Isabelle Vila, Clara Taffoni, Andrei Turtoi, Nadine Laguette

### ► To cite this version:

Hanane Chamma, Isabelle Vila, Clara Taffoni, Andrei Turtoi, Nadine Laguette. Activation of STING in the pancreatic tumor microenvironment: a novel therapeutic opportunity. *Cancer Letters*, 2022, 538, pp.215694. 10.1016/j.canlet.2022.215694 . hal-03668657

**HAL Id: hal-03668657**

**<https://hal.science/hal-03668657v1>**

Submitted on 15 May 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

**Title:** Activation of STING in the pancreatic tumor microenvironment: a novel therapeutic opportunity

**Authors:** Hanane Chamma<sup>1</sup>, Isabelle Vila<sup>1</sup>, Clara Taffoni<sup>1</sup>, Andrei Turtoi<sup>2\*</sup>, Nadine Laguette<sup>1\*</sup>

**Affiliations:**

<sup>1</sup> Institut de Génétique Humaine, CNRS, Université de Montpellier, Molecular Basis of Inflammation Laboratory, Montpellier, France

<sup>2</sup> Tumor Microenvironment Laboratory, Institut de Recherche en Cancérologie de Montpellier, Université de Montpellier, INSERM U1194, 34000 Montpellier, France

\* To whom correspondence should be addressed

**Correspondence:** [Andrei.turtoi@inserm.fr](mailto:Andrei.turtoi@inserm.fr) ; [Nadine.laguette@igh.cnrs.fr](mailto:Nadine.laguette@igh.cnrs.fr)

**Abstract**

Pancreatic ductal adenocarcinoma (PDAC) is a cancer of poor prognosis that presents with a dense desmoplastic stroma that contributes to therapeutic failure. PDAC patients are mostly unresponsive to immunotherapy. However, hopes to elicit response to immunotherapy have emerged with novel strategies targeting the Stimulator of Interferon Genes (STING) protein, which is a major regulator of tumor-associated inflammation. Combination of STING agonists with conventional immunotherapy approaches has proven to potentiate therapeutic benefits in several cancers. However, recent data underscore that the output of STING activation varies depending on the cellular and tissue context. This suggests that tumor heterogeneity, and in particular the heterogeneity of the tumor microenvironment (TME), is a key factor determining whether STING activation would bear benefits for patients.

In this review, we discuss the potential benefits of STING activation in PDAC. To this aim, we describe the major components of the PDAC TME, and the expected consequences of STING activation.

**Key words:** *STING, inflammation, tumor microenvironment, pancreatic cancer, immunotherapy*

## I. INTRODUCTION

---

**Abbreviations:** PDAC, Pancreatic ductal adenocarcinoma; STING, Stimulator of Interferon Genes; cGAS, cyclic GMP-AMP cGAMP synthase; TME, Tumor microenvironment; CDNs, Cyclic dinucleotides; DCs, Dendritic cells; MDSC, Myeloid-derived suppressor cells; NK, Natural killer; CAFs, Cancer-associated fibroblasts; iCAFs, inflammatory CAFs; DMXAA, 5,6-dimethylXAA (xanthenone-4-acetic acid); Tregs, regulatory T cells.

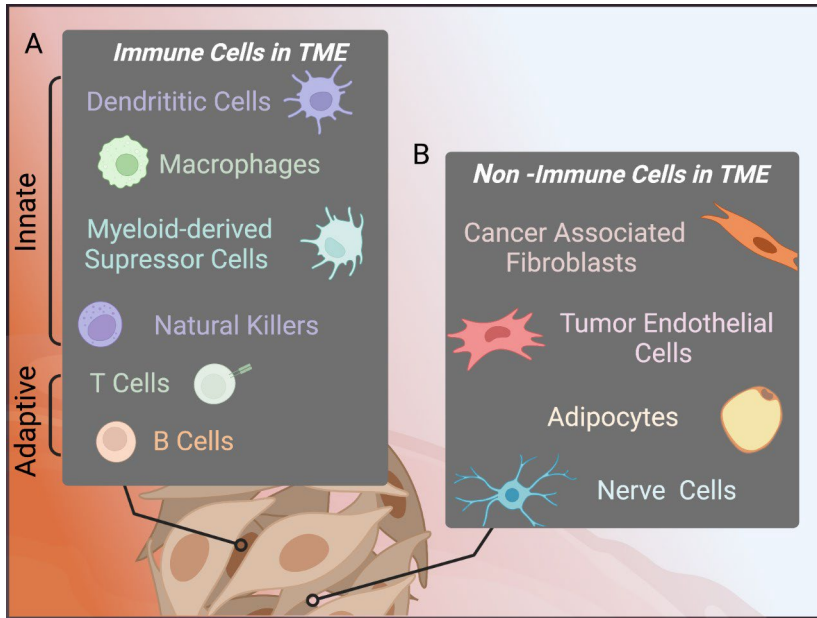
Pancreatic cancer is one of the most aggressive solid tumors with high mortality and morbidity rates [1]. The prevailing form of pancreatic cancer is pancreatic ductal adenocarcinoma (PDAC) which accounts for more than 90% of cases [2]. The care of PDAC patients presents high unmet needs and major space for improvement. Indeed, contrary to several major cancers for which significant progress has been made in recent years, PDAC is projected to become the second leading cause of cancer-related deaths within the next two decades [1]. Additionally, PDAC patients have not benefited from recent advances in immunotherapy-based cancer treatments, as they are largely unresponsive to single agent immunotherapy [1]. The poor responsiveness of PDAC to treatments can be, to a large extent, attributed to late diagnosis, with most patients presenting locally advanced or metastatic tumors which are profoundly immunosuppressed and embedded in a dense desmoplastic stroma that restrains drug accessibility [1, 3]. Breaching through the stroma, modulating its composition, and permitting reactivation of PDAC immunogenicity could thus allow overcoming treatment resistance.

New therapeutic hopes have emerged in recent years, with the identification of a novel target protein that can promote reactivation of anti-tumor responses. Indeed, the Stimulator of Interferon Genes (STING) adaptor protein has been identified as a central player in the initiation of cancer-related inflammation that in turn promotes anti-tumor responses. STING is a scaffold protein that is activated upon interaction with cyclic dinucleotides (CDN) such as those produced by the cyclic GMP-AMP (cGAMP) synthase (cGAS) [4]. cGAS-dependent cGAMP production [4] is triggered following interaction of cGAS with cytosolic pathological nucleic acids, including double stranded DNA (dsDNA), single stranded DNA (ssDNA) and RNA:DNA hybrids [5, 6]. The interaction of cyclic nucleotides with STING promotes its dimerization and recruitment of kinases and transcription factors [7] that concertedly orchestrate the production of a subset of inflammatory cytokines and of type I Interferons (IFN $\alpha$  and  $\beta$ ) [7]. The expression of this panel of cytokines in turn influences the recruitment and activation of cells of the adaptive immune system, including cytotoxic CD8<sup>+</sup> T cells that bear anti-tumoral properties. Consequently, tremendous research efforts have emerged to identify STING agonists, with the aim to reactivate tumor immunogenicity and the hope for combination strategies with immunotherapies.

Ample experimental evidence suggest that treatment with STING agonists may benefit PDAC patients [8]. However, there is growing evidence that STING activation (i) does not bring the same outcomes, depending on cell type-, tissue-, or species-specific parameters (ii) may promote side-effects, and (iii) may in fact result in adverse immunosuppressive outcomes, such parameters should not be overlooked. Within the present review, we discuss how tumor heterogeneity in PDAC represents a major obstacle for therapies, and review the impact of STING activation in this context. Finally, we examine how combining STING agonists to immunotherapy regimens, may – or may not – benefit PDAC patients.

## **II. PDAC tumor heterogeneity: a major obstacle to current therapies**

One of the best documented challenges in the treatment of PDAC is resistance to chemotherapy regimens, notably because of limited drug accessibility, a parameter which is intrinsically linked to the composition of the PDAC tumor microenvironment (TME) [3]. Indeed, the PDAC TME is highly fibrotic and poorly vascularized, hindering efficiency of immunotherapy. In addition, the PDAC landscape is profoundly immunosuppressed with decreased immune infiltration, rendering therapeutic strategies targeting immune cells poorly effective [3]. Concerted analysis of PDAC TME composition, comprised of immune (Figure 1A) and non-immune (Figure 1B) cells is paramount to understanding and overcoming treatment resistance.



**Fig. 1: Schematic representation of the immune and non-immune cells present in the PDAC stroma and which are discussed in the present review.** (A) The immune cells associated with PDAC stroma. There are two existing subtypes: (i) innate immune cells including Dendritic cells, Macrophages (M2 like macrophages), Myeloid-derived suppressor cells, and Natural Killer cells. (ii) adaptive immune cells including T and B cells. (B) The non-immune cells associated with PDAC stroma. There are four major existing cell types including Cancer-Associated Fibroblasts, Tumor Endothelial cells, Adipocytes, and nerve cells. Created with Biorender.com.

## II.1. Role of immune cells in the PDAC TME

### II.1. i. The innate immune infiltrate of PDAC

Innate immune cells of myeloid origin, such as dendritic cells (DCs) and macrophages, play a key role in the initiation of anti-tumor responses. They are involved in the detection of cancer cells, initiation and maintenance of inflammatory responses, and priming of adaptive immunity.

In the PDAC landscape, those innate immune cells mostly present immunosuppressive phenotypes [9]. Indeed, macrophages in the PDAC TME have been found to be mostly alternatively activated in the M2 immunosuppressive subtype that promotes tumor growth [10]. High levels of M2 macrophages in PDAC patients are associated with shorter survival [11]. Testament to the pivotal role of these cells in determining PDAC tumor fate, there is evidence that modulating the polarization status of macrophages may benefit PDAC patients. Indeed, decreased M2 macrophages infiltration in the TME of PDAC animal models, leads to tumor regression and T cell reactivation [12]. In addition, chemotherapy-induced M2 to M1 macrophage repolarization in PDAC patients correlates with better survival [13].

Similarly, Myeloid-Derived Suppressor Cells (MDSCs), immature DCs and granulocytes, are present at high levels in the PDAC TME [14] where they can induce T cell exhaustion while reducing T cell-induced cytokine production and promoting T cell apoptosis [15]. Additionally, MDSCs can directly activate regulatory T cells (Tregs) that in turn inhibit T cell activation, favoring PDAC progression [16]. Interestingly, the deficient priming of tumor-specific adaptive responses,

due to the immature state of DCs in PDAC, can be overcome by DCs vaccine in PDAC mouse models [17].

In parallel, there is a marked decrease in immune cell populations that would promote anti-tumor responses. For instance, the NK infiltrate is reduced in PDAC patients [18] and the cytotoxic function of circulating NK cells is impaired [18]. While stimulating the cytotoxic activity of NK cells in murine models of PDAC [19] and in patients [20] correlated with longer survival.

### **II.1. ii. The adaptive immune cells of PDAC TME**

PDAC patients with high CD8+ and CD4+ levels have better survival rates [21]. However, T cells, and in particular cytotoxic CD8+ T cells, are mostly exhausted within the PDAC TME [22]. Such exhaustion can be, at least in part, attributed to tumor cells expressing checkpoint inhibitors, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) which, combined to the recruitment of innate immunosuppressive cells, restricts the infiltration of effector T cells [23] and limits T cell expansion [16].

In further agreement with the immunosuppressed characteristic of PDAC tumors, Tregs are often found associated with PDAC tumors [23, 24]. Tregs block DCs maturation, reducing their capacity to present tumor antigens to T cells, consequently impeding anti-tumor responses [25]. Additionally, Tregs increase the expression of programmed death ligand-1 (PD-L1) checkpoint inhibitor on DCs, thus promoting T cell inactivation. However, testament to the pivotal role of the interplay between Tregs and DCs in PDAC fate, blocking PD-L1 improved the tumor response in PDAC xenograft models, by increasing T cell activation [26].

Intriguingly, B lymphocytes in the PDAC TME are found to be highly reactive and implicated in the production of inflammatory cytokines and chemokines [27]. Although in the case of PDAC increased B cell density has been shown to predict longer survival [13], it is not clear how they contribute to PDAC treatment resistance.

In sum, the immune infiltrate of PDAC comprises a large set of immunosuppressive immune cells while effector CD4+ and CD8+ T cells are scarce [21, 24]. Immune activation in the PDAC landscape therefore appears as a promising therapeutic avenue.

## **II.2. Role of non-immune cells in PDAC TME**

A large part of the PDAC TME is comprised of non-immune cell subpopulations, including cancer-associated fibroblasts (CAFs), tumor endothelial cells, cancer-associated adipocytes and neuronal cells, which may contribute to define the immunosuppressive nature of the TME.

### **II.2.i. Cancer-associated fibroblasts: heterogeneity in origin and function**

CAFs, which originate mostly from stellate cells in PDAC, account for up to 90% of the total PDAC mass [28, 29]. Studies suggest the presence of two major subtypes of CAFs in the PDAC TME. First, the myCAF subtype, presenting myofibroblastic characteristics, are located close to neoplastic tumor cells and are responsible for the formation of the desmoplastic stroma [30]. Second, inflammatory CAFs (iCAFs), that have lost their myofibroblastic characteristics, are distant from the tumor and are responsible for the secretion of a vast array of soluble factors that concertedly promote immunosuppression in the PDAC TME [30]. myCAF and iCAFs cooperate to promote PDAC progression and hamper efficient treatment [31].

Recent single-cell studies have found additional, less abundant, CAF subpopulations that also influence PDAC progression. For example, CD105 negative (CD105neg) CAFs have been shown to promote the infiltration of effector CD8+ T cells, T cell memory precursor development, DCs infiltration, and antigen presentation [32]. Antigen-presenting CAFs (apCAFs), which express major histocompatibility complex (MHC) class II antigen presentation machinery, but lack the co-

stimulatory molecules, have been shown to bear the capacity to activate CD4<sup>+</sup> T cells [33]. Thus, contrary to myCAF and iCAF, these two subpopulations can be expected to promote anti-tumor immunity. Owing to the presence of these antagonistic CAF subpopulations in the PDAC TME, the impact of treatments targeting CAFs indiscriminately is difficult to anticipate.

### **II.2.ii. Other tumor-supporting cells**

While CAFs and immune cells are the two major components of the TME and influence directly tumor immunogenicity, additional cells are present in the PDAC stroma and may be important when therapies targeting the cGAS-STING pathway are considered. Amongst the tumor-associated cells that are of importance in this context are endothelial cells, adipocytes and nerve cells.

#### **Tumor endothelial cells**

Endothelial cells are major STING expressers. Tumor cells interact with endothelial cells, during angiogenesis, primarily to ensure oxygen and nutrient supply to the tumor. However, tumor endothelial cells also shape the overall PDAC tumor microenvironment, notably by acting as a selective barrier that governs immune cells' access to the tumor site [34]. Tumor endothelial cells can therefore regulate the amplitude and the efficacy of anti-tumor responses [7]. For further insight on the role of tumor endothelial cells in TME, refer to Nagl et al. [35].

#### **Adipocytes**

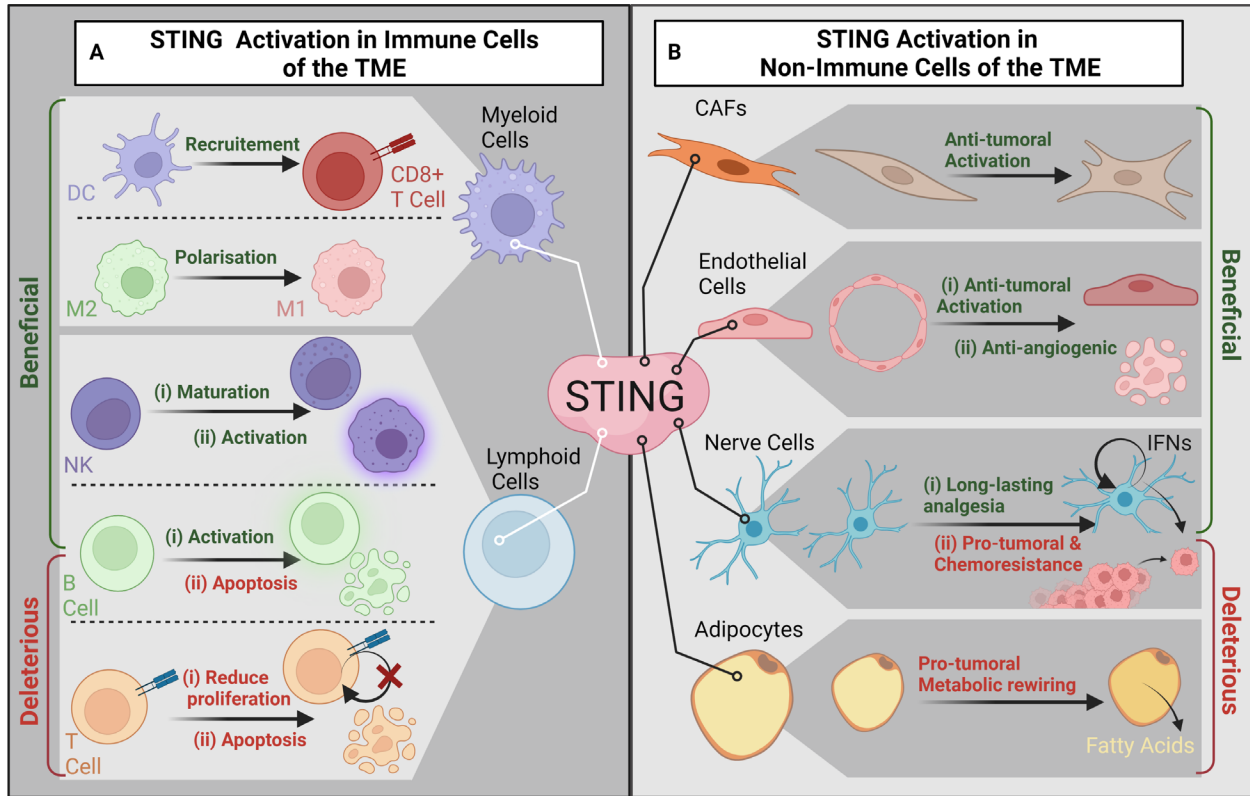
Adipocytes present in the TME remain poorly studied, despite their contribution to several aspects of tumorigenesis and their documented crosstalk with tumor cells [36]. Cancer cells, including pancreatic cancer cell lines, can induce dedifferentiation of adipocytes into cancer-associated adipocytes [37]. Cancer-associated adipocytes are characterized by a loss in mature adipocytes markers and a gain in fibroblastic markers, and exhibit two major functions. First, they release tumor-promoting soluble factors including pro-inflammatory cytokines and chemokines that enable PDAC progression [38]. Second, cancer-associated adipocytes can support metabolic rewiring of cancer cells by providing nutrients. In support, Meyer *et al.* showed that the secretion of glutamine, a derivative from the catabolism of lipid stores, by cancer associated adipocytes induces PDAC cell proliferation [39]. Cancer-associated adipocytes may therefore play important roles in defining PDAC progression.

#### **Neurons**

The PDAC TME features a rather dense neuronal cell component and PDAC cancer cells have been shown to have a “tropism” for nerve cells. Cancer cells are frequently grouped along nerve fibers, forming structures that are referred to as per-neuronal invasions [40]. This association between nerve and cancer cells is characterized by a rich cytokine-mediated crosstalk. In the context of the present review, it is worth noting that cancer cells interaction with nerves has a significant impact on, and is controlled by, the immunological component of the TME. Cavel *et al.* have shown that endoneurial macrophages, which are found in the proximity of per-neuronal invasions, stimulate the formation of this structure [40] and while promoting the recruitment of inflammatory monocytes. These differentiate into macrophages and potentiate per-neuronal invasions nerve invasion by cancer cells [41]. Evidence from other organs than the pancreas suggests that nerve cells in the PDAC TME may have even more critical roles in establishing a tumor-permissive immune-microenvironment. Namely, in breast cancer, nerve density correlates with the expression of immune checkpoint molecules (PD-1, PD-L1) and is indicative of patient prognosis [42].

### **III. STING activation in PDAC: good or bad?**

Several studies in mice demonstrate that STING agonists can reactivate PDAC immunogenicity. The rationale for STING activation in cancer primarily relies on its ability to activate immune cells and trigger inflammatory responses. Consequently, STING agonists can promote anti-tumor immune responses and strengthen immunotherapies. However, STING expression is not restricted to immune cells and within the TME, it may also be expressed in stromal and cancer cells. Below, we examine what is known about the consequences of STING activation in the cells composing the PDAC TME (Fig. 2).



**Fig. 2: Impact of STING agonists in immune and non-immune cells of the PDAC microenvironment.** (A) **Impact of STING agonists in immune cells.** From top to bottom: In myeloid cells, STING activation in DCs favors CD8+ T cells recruitment and repolarizes the pro-tumoral M2-macrophages, into anti-tumoral M1 macrophages. In lymphoid cells, STING agonists enhance the maturation and activation of NK and B cells, but reduce the proliferation of B Lymphocytes and reduce proliferation and induce apoptosis of T cells. (B) **Impact of STING Agonists in non-immune cells.** From top to bottom: In non-immune cells, STING agonists promote the activation of anti-tumoral responses in CAFs and endothelial cells while lowering vascular density. In contrast, STING agonists lead to pro-tumoral responses in nerve cells and adipocytes, involving STING-dependent chemoresistance in nerve cells and metabolic rewiring in adipocytes. In green: Impact of STING activation at cellular level that can be expected to be beneficial for patient outcome. In red: Impact of STING activation at cellular level that can be expected to be deleterious for patient outcome. White connectors from STING indicate the immune cells of the PDAC TME, black connectors indicate the non-immune cells of the PDAC TME. Created with Biorender.com.

### III.1. STING activation in immune cells: inflammation-related or not?

#### STING activation in myeloid cells

STING is abundantly expressed in myeloid cells and the role of STING activation in myeloid cells and its impact on PDAC has been well explored [43-45] (Fig. 2A). STING activation in tumor-resident antigen presenting cells (APCs) is shown to be required to induce antitumor CD8+ T-cell response *in vivo* [44] and STING stimulation using a synthetic cyclic dinucleotide derivative induces activation of DCs in draining lymph nodes [45]. Moreover, STING activation in macrophages can promote repolarization of immunosuppressive M2 macrophages towards anti-tumor M1 phenotype [45]. This suggests that repolarization of M2-like macrophages into M1 Macrophages may contribute to the anti-tumor efficacy of CDNs in tumors with high myeloid infiltrates. Finally, STING-activating CDN can also reduce the immunosuppressive function of the MDSCs [46]. However, STING activation also promotes the infiltration of immunosuppressive cells, including the MDSCs, into tumors [47], although this latter effect may be indirect.

### **STING activation in lymphoid cells**

The consequences of STING activation in lymphoid cells remains debated (Fig. 2A). Type I Interferons (IFNs) are known to regulate NK cell biology and their anti-tumor activity [48], suggesting that STING activation may promote NK activation. Indeed, Nicolai *et al* showed that CDN treatment results in NK cell activation and tumor clearance [49]. Moreover, STING agonists promote NK cytotoxicity and induce tumor rejection in many tumor models [49, 50]. Inducing type I IFN production in PDAC tumors also enhanced the anti-PDAC activity of cytotoxic NK cells [51], whereas lack of type I IFN impaired NK maturation and cytotoxicity [52]. Altogether, these reports support that STING activation and type I IFNs enhance NK cells anti-tumor activity.

To the opposite of these potential beneficial outcomes of STING activation in NK cells, STING activation in T cells appears less enticing. Indeed, STING activation has been shown to reduce proliferation and promote apoptosis of T cells [53]. Additionally, mutation leading to constitutive STING activation (STING V155M) led to reduced T cell expansion, proliferation and elevated apoptosis [54]. These effects were counteracted by expression of the R71H-G230A-R293Q (HAQ) common STING allele [55] in an IFN-independent manner [54]. Thus, STING is a negative regulator of T cell proliferation [54], implying that following STING activation, which leads to its degradation [56], this regulation would be lost. Yet, the consequences on T cell activity in the context of tumors remain unknown.

In B cells, constitutive expression of STING by genetic engineering or treatment with STING agonists both result in degradation of membrane-bound immunoglobulins and increase the rate of malignant B lymphocyte apoptosis [57]. CDNs also activate the responses of normal B cell *in vitro* and *in vivo* leading to a CDN-enhanced antibody production [58]. Moreover, it has also been shown that type I IFN increases the survival of B cells by protecting resting B cells from apoptosis [59]. The impact on STING activation in B cells present in the PDAC TME that are active remains unknown.

Therefore, while STING agonists promote innate immune activation, their impact on adaptive immunity remains difficult to appreciate, and could be expected to bring deleterious outcomes.

### **III.2. STING activation in the tumor non-immune microenvironment: the unknown?**

The impact of STING activation in non-immune cells in the PDAC TME remains poorly studied (Fig. 2B), but extrapolation from other cancer types suggest that the outcome is likely to be difficult to predict.

### **STING activation in CAFs**



The presence of high levels of Interferon regulatory factor 3 (IRF3) in the nuclei of CAFs predicts that STING is activated in CAFs [60]. Indeed, IRF3 is a transcription factor activated downstream of STING and that translocates to the nucleus to promote the transcription of type I IFNs and STING-dependent cytokines. It was shown that the transfer of cytosolic material from cancer cells to CAFs can fuel cGAS-dependent cGAMP production, subsequent STING activation and anti-tumor responses [60]. However, the impact of STING activation in the different CAF subtypes described in PDAC is as of today not elucidated.

### **STING activation in endothelial cells**

Endothelial cells have been shown to govern type I IFN production in response to cGAMP injection *in vivo* and *ex vivo* [61]. Indeed, endothelial cells produce type I IFNs upon intratumoral injection of STING agonists in multiple mouse tumor models [61]. Moreover, STING agonists or cGAMP injections consistently lowered hypoxia indicators and vascular density, while increasing intratumoral CD8+ T cell infiltration and slowing tumor growth. These effects are dependent on STING expression in cells of the microenvironment, and were lost in STING-deficient mice [62]. Of note, 5,6-dimethylXAA (xanthenone-4-acetic acid) (DMXAA) or other STING agonists was initially designed as an anti-vascular agent [9], indeed, several studies in mice have shown that DMXAA promotes inhibition of vascular endothelial growth factor receptor (VEGFR) tyrosine kinases [63]. In agreement, treating tumors with the DMXAA STING agonist led to a decrease in tumor vessel density thus promoting restoration of vessel structure and function, together with tumor regression [62]. Thus, it is unclear how much of the impact of DMXAA during tumorigenesis is linked to type I IFN production or to anti-angiogenic effects.

### **STING activation in adipocytes: impact on lipid metabolism?**

STING was shown to be involved in obesity-induced inflammation. Indeed, high-fat diet feeding of mice induces mitochondrial DNA release in the cytosol of adipocytes, leading to STING activation [64]. More recently, STING was also shown to directly inhibit lipid metabolism independently of its immune function [65], and alters the expression of the immune response genes [66]. This role of STING could be important in adipocytes, which are the main cells involved in the lipid storage and metabolic rewiring of cancer cells by providing nutrients, but the non-immune function of STING has not been studied in cancer cells. Interestingly several cancer types have been documented to downregulate STING [67]. This may indicate that these cancer cells downregulating STING to avoid immune system activation might also benefit from lipid metabolism reprogramming for their proliferation and invasion. In addition, the chronic use of STING agonist as an immunostimulatory adjuvant, could be expected to lead to decreased STING levels in cancer cells in turn promoting metabolic rewiring that may favor cancer proliferation [68]. Therefore, STING agonists might induce metabolic side effects, the latter is yet to be investigated in PDAC.

### **STING in neurons: a way to alleviate PDAC-associated pain?**

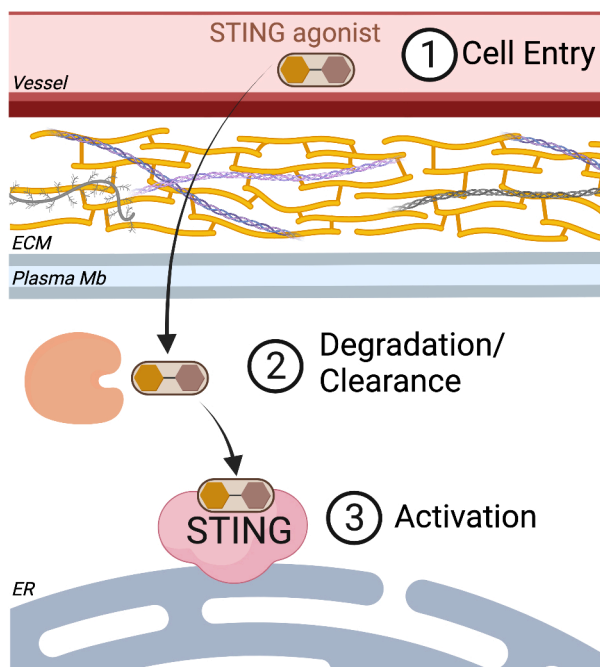
A common symptom in PDAC patients is unmanageable pain, which has been associated with perineural invasion by cancer cells [69]. It was recently demonstrated that STING is a critical regulator of nociception [70]. Indeed, STING agonists provide long-lasting analgesia and suppress nociception in a murine model chemotherapy-induced peripheral neuropathy [70]. This role of STING and type I IFN in inhibiting pain could help alleviate cancer-associated pain [70]. However, STING activation in neuronal cells may also lead to adverse outcomes. For instance, it was reported that metastatic brain cancer cells transfer cGAMP to astrocytes, leading to STING activation that, in this context, promotes tumor growth and chemoresistance [71]. Thus, close examination of the impact of STING activation in neurons and supporting cells is required before clinical applications could be envisioned.

While targeting the TME is a therapeutic approach gaining growing interest [12], our understanding of the consequences of STING activation in non-immune cells of the TME remains sketchy.

### III.3. STING agonists as a therapeutic option.

#### STING agonist delivery challenge

While the physicochemical properties of STING agonists have long hampered their clinical use [72], novel molecules now allow systemic administration [73]. Indeed delivering STING agonists *in vivo*, most of which being highly hydrophilic, has been challenging as the plasma membrane is highly hydrophobic [74]. Additionally, hydrolases have been described to readily degrade cGAMP [75]. To overcome these issues, allow crossing the plasma membrane while protecting STING agonists from degradation and slowing-down their clearance, several delivery systems have been designed, including liposomes [76], hydrogels [77] or polymers [78]. Moreover, new synthetic STING agonists [79] present a U-shaped conformation (e.g. E7766) or antibody-coupling (e.g. TAK 500) that enhance cell permeability and *in vivo* potency. (Figure 3)



**Fig. 3: Schematic representation of the challenges associated with STING agonist administration.** To reach their target, STING agonists must (1) cross the extracellular matrix (ECM) and the Plasma membrane (Mb). Once in the cytosol, (2) they must be resistant to degradation/clearance by nucleases. STING agonists modified to meet these criteria should (3) retain the ability to activate STING. Created with Biorender.com.

#### STING agonists in clinical trials

The anti-tumoral activity of STING agonists observed in many studies has led to the development of various STING agonists currently used in clinical trials [80], some of which already bringing promising results [81]. The DMXAA STING agonist was initially broadly used in first pre-clinically studies. However, it was shown to be mouse STING-specific [82] leading to null effect in human [83]. In recent years, many efforts have been made to develop efficient, stable and human-specific STING agonists. Two major classes of STING agonists are currently under development:

synthetic CDN that mimic the natural STING ligand, and non-CDN agonists [8]. Currently, several CDN and non-CDN agonists are being tested in clinical trials, mostly in combination therapies (Table I). Indeed, STING activation boosts immune responses and enhances existing cancer therapy efficiency – in particular immunotherapy.

Recent improvements in STING agonist delivery routes, coupled to the fact that STING agonists have been proven efficient as adjuvants to immunotherapies [8, 37], raise the hope that they may benefit PDAC patients. Indeed, STING agonists have been shown to boost the activity of immune checkpoint blockade-based immunotherapy approaches in different tumors [84], including PDAC [85]. Moreover, combining Chimeric antigen receptor (CAR) T immunotherapy [37] with STING agonist produces synergistic effect on antigen presenting cell activation in mice where PDAC tumor cells were orthotopically transplanted [86]. Although several clinical trials (Table I) are now ongoing to assess the efficiency of combining immunotherapy with STING agonist in solid tumors or lymphoma, it is important to bear in mind that careful assessment at the cellular level of the impact of such combination therapies is crucial. In addition, in several instances, STING agonists have been tested in combination with chemotherapy or radiotherapy [87]. Since recent evidences point towards a role for cGAS and STING in controlling DNA repair outcomes [88, 89], particular attention has to be taken when combining genotoxic agents and STING agonists.

**Table I:** Main on-going clinical trials using STING agonists in oncological indications.

Agonist	Class	Cancer condition	Status	Phase	Co-therapy	NCT Number
<b>BI 1387446</b>	CDN	▫Neoplasms	Recruiting	I	None	NCT04147234
<b>BMS- 986301</b>	CDN	▫Advanced Solid Cancers	Recruiting	I	Nivolumab/ Ipilimumab	NCT03956680
<b>E7766</b>	Non- CDN	▫Lymphoma ▫Advanced Solid Tumors	Recruiting	I	None	NCT04144140
<b>GSK374 5417</b>	Non- CDN	▫Neoplasms	Recruiting	I	Dostarlimab	NCT03843359
<b>MK- 1454</b>	CDN	▫Solid Tumors Lymphoma	Active, not recruiting	I	Pembrolizumab	NCT03010176
<b>MK- 1454</b>	CDN	▫Head and Neck Squamous Cell Carcinoma (HNSCC)	Active, not recruiting	II	Pembrolizumab	NCT04220866
<b>MK- 2118</b>	Non- CDN	▫Solid Tumor ▫Lymphoma	Recruiting	I	Pembrolizumab	NCT03249792
<b>SB1128 5</b>	CDN	▫Melanoma ▫Head and Neck Squamous Cell Carcinoma	Recruiting	I	Atezolizumab	NCT04096638

▫Solid Tumor						
<b>SNX281</b>	Non-CDN	▫Advanced Solid Tumor ▫Advanced Lymphoma	Not yet recruiting	I	Atezolizumab / Tiragolumab	NCT04609579
<b>TAK-500</b>	Non-CDN	▫Pancreatic Cancer ▫Hepatocellular Cancer ▫Squamous Cell Cancer (SCC) (and 5 more...)	Not yet recruiting	I	Pembrolizumab	NCT05070247
<b>TAK-676</b>	Non-CDN	▫Solid Neoplasms	Recruiting	I	Pembrolizumab	NCT04420884
<b>TAK-676</b>	Non-CDN	▫Carcinoma, Non-Small-Cell Lung ▫Triple Negative Breast Neoplasms ▫Squamous Cell Carcinoma of Head and Neck	Recruiting	I	Pembrolizumab	NCT04879849
<b>TAK-676</b>	Non-CDN	▫Solid Tumor	Recruiting	I	▫Carboplatin ▫5-FU (and 9 more...)	NCT04541108

## VI. DISCUSSION

The objective of cancer immunotherapy is to harness the host immune system in order to eliminate tumor cells. Although single-agent immunotherapy is ineffective in PDAC, there is evidence for a weak, but significant, benefit in combination with chemotherapy in patients that have undergone surgical resection of the tumor [73], suggesting that this therapeutic avenue may still be explored.

Even though STING agonist bears promising therapeutics perspectives, there are well-documented reports about potential negative impacts of long-term STING activation, including impairment of long-term immunological memory [10]. Moreover, in certain context, STING has been described to promote tumorigenesis and chemoresistance [90]. Furthermore, STING activation is tightly regulated at several levels, including post-translational modifications, such as phosphorylation or ubiquitination, but also through modulation of STING association with its ligands [6, 65]. It is also growingly clear that STING levels are regulated in a cell type-specific manner [91]. While downregulation of STING levels is well-documented in pathological situations, what governs homeostatic cell type-specific STING downregulation remains poorly understood. Moreover, STING polymorphisms exist in the human population affecting protein level, activation and sensitivity to agonists [55]. In this context, the impact of STING agonists on cells that express low (or no) STING should be carefully examined. The consequences of STING agonists

administration on cells other than myeloid are just starting to emerge. As described in this review, while STING activation promotes myeloid cells maturation, differentiation, cross-presentation [45, 46], it has cytostatic effects on T cells [54]. Such anti-proliferative properties may prevent adequate adaptive immune responses. Yet, in murine PDAC models, STING activation leads to T cell infiltration, expansion and priming together with DCs maturation [44, 45, 62, 91] and repolarization of M2 immuno-suppressive macrophages into the M1 pro-inflammatory macrophages [45]. While the impact on other components of the PDAC TME necessitates a detailed characterization, this raises the hope that STING-targeting therapies may reactivate PDAC immunogenicity.

### Acknowledgement and Funding

We thank Johanna Marines for reading of the manuscript. Work in N.L.'s laboratory is supported by the European Research Council (ERC-Stg CrIC: 637763 , ERC-PoC DIM-CrIC: 893772 ), la Ligue pour la Recherche contre le Cancer, La Région Occitanie, the Centre Nationale de la Recherche Scientifique (CNRS – prematuration program) and the Agence Nationale de Recherche sur le Sida et les Hépatites Virales (ANRS: ECTZ117448 ). H.C. is supported by a PhD fellowship from la Ligue pour la Recherche contre le Cancer. C.T. is supported by an ANRS fellowship (ECTZ119088). I.K.V. is supported by the Fondation pour la Recherche Médicale (ARF20170938586). AT acknowledges LabEx MABImprove for financial support. Schematic representations were created with <https://biorender.com/>.

### References:

1. Elsayed, M. and M. Abdelrahim, *The Latest Advancement in Pancreatic Ductal Adenocarcinoma Therapy: A Review Article for the Latest Guidelines and Novel Therapies*. Biomedicines, 2021. **9**(4).
2. Collisson, E.A., et al., *Molecular subtypes of pancreatic cancer*. Nat Rev Gastroenterol Hepatol, 2019. **16**(4): p. 207-220.
3. Dougan, S.K., *The Pancreatic Cancer Microenvironment*. Cancer J, 2017. **23**(6): p. 321-325.
4. Sun, L., et al., *Cyclic GMP-AMP synthase is a cytosolic DNA sensor that activates the type I interferon pathway*. Science, 2013. **339**(6121): p. 786-91.
5. Ishikawa, H., Z. Ma, and G.N. Barber, *STING regulates intracellular DNA-mediated, type I interferon-dependent innate immunity*. Nature, 2009. **461**(7265): p. 788-92.
6. Guerra, J., et al., *Lysyl-tRNA synthetase produces diadenosine tetraphosphate to curb STING-dependent inflammation*. Sci Adv, 2020. **6**(21): p. eaax3333.
7. Carman, C.V. and R. Martinelli, *T Lymphocyte-Endothelial Interactions: Emerging Understanding of Trafficking and Antigen-Specific Immunity*. Front Immunol, 2015. **6**: p. 603.
8. Amouzegar, A., et al., *STING Agonists as Cancer Therapeutics*. Cancers (Basel), 2021. **13**(11).
9. Ching, L.M., et al., *Induction of endothelial cell apoptosis by the antivascular agent 5,6-Dimethylxanthenone-4-acetic acid*. Br J Cancer, 2002. **86**(12): p. 1937-42.
10. Chabanon, R.M., et al., *PARP inhibition enhances tumor cell-intrinsic immunity in ERCC1-deficient non-small cell lung cancer*. J Clin Invest, 2019. **129**(3): p. 1211-1228.
11. Ino, Y., et al., *Immune cell infiltration as an indicator of the immune microenvironment of pancreatic cancer*. Br J Cancer, 2013. **108**(4): p. 914-23.
12. Candido, J.B., et al., *CSF1R(+) Macrophages Sustain Pancreatic Tumor Growth through T Cell Suppression and Maintenance of Key Gene Programs that Define the Squamous Subtype*. Cell Rep, 2018. **23**(5): p. 1448-1460.
13. Castino, G.F., et al., *Spatial distribution of B cells predicts prognosis in human pancreatic adenocarcinoma*. Oncoimmunology, 2016. **5**(4): p. e1085147.
14. Pergamo, M. and G. Miller, *Myeloid-derived suppressor cells and their role in pancreatic cancer*. Cancer Gene Ther, 2017. **24**(3): p. 100-105.
15. Tao, J., et al., *CD8(+) T cells exhaustion induced by myeloid-derived suppressor cells in myelodysplastic syndromes patients might be through TIM3/Gal-9 pathway*. J Cell Mol Med, 2020. **24**(1): p. 1046-1058.

16. Siret, C., et al., *Deciphering the Crosstalk Between Myeloid-Derived Suppressor Cells and Regulatory T Cells in Pancreatic Ductal Adenocarcinoma*. *Front Immunol*, 2019. **10**: p. 3070.
17. Yang, J., et al., *Effect of route of administration on the efficacy of dendritic cell vaccine in PDAC mice*. *Am J Cancer Res*, 2020. **10**(11): p. 3911-3919.
18. Marcon, F., et al., *NK cells in pancreatic cancer demonstrate impaired cytotoxicity and a regulatory IL-10 phenotype*. *Oncoimmunology*, 2020. **9**(1): p. 1845424.
19. Xie, X., et al., *Polysaccharide enhanced NK cell cytotoxicity against pancreatic cancer via TLR4/MAPKs/NF- $\kappa$ B pathway in vitro/vivo*. *Carbohydr Polym*, 2019. **225**: p. 115223.
20. Van Audenaerde, J.R.M., et al., *Interleukin-15 stimulates natural killer cell-mediated killing of both human pancreatic cancer and stellate cells*. *Oncotarget*, 2017. **8**(34): p. 56968-56979.
21. Carstens, J.L., et al., *Spatial computation of intratumoral T cells correlates with survival of patients with pancreatic cancer*. *Nat Commun*, 2017. **8**: p. 15095.
22. Papalampros, A., et al., *Unique Spatial Immune Profiling in Pancreatic Ductal Adenocarcinoma with Enrichment of Exhausted and Senescent T Cells and Diffused CD47-SIRP $\alpha$  Expression*. *Cancers (Basel)*, 2020. **12**(7).
23. Tang, Y., et al., *An increased abundance of tumor-infiltrating regulatory T cells is correlated with the progression and prognosis of pancreatic ductal adenocarcinoma*. *PLoS One*, 2014. **9**(3): p. e91551.
24. Amedei, A., et al., *Ex vivo analysis of pancreatic cancer-infiltrating T lymphocytes reveals that ENO-specific Tregs accumulate in tumor tissue and inhibit Th1/Th17 effector cell functions*. *Cancer Immunol Immunother*, 2013. **62**(7): p. 1249-60.
25. Jang, J.E., et al., *Crosstalk between Regulatory T Cells and Tumor-Associated Dendritic Cells Negates Anti-tumor Immunity in Pancreatic Cancer*. *Cell Rep*, 2017. **20**(3): p. 558-571.
26. Azad, A., et al., *PD-L1 blockade enhances response of pancreatic ductal adenocarcinoma to radiotherapy*. *EMBO Mol Med*, 2017. **9**(2): p. 167-180.
27. Minici, C., et al., *B lymphocytes contribute to stromal reaction in pancreatic ductal adenocarcinoma*. *Oncoimmunology*, 2020. **9**(1): p. 1794359.
28. Hosein, A.N., R.A. Brekken, and A. Maitra, *Pancreatic cancer stroma: an update on therapeutic targeting strategies*. *Nat Rev Gastroenterol Hepatol*, 2020. **17**(8): p. 487-505.
29. Kalluri, R., *The biology and function of fibroblasts in cancer*. *Nat Rev Cancer*, 2016. **16**(9): p. 582-98.
30. Öhlund, D., et al., *Distinct populations of inflammatory fibroblasts and myofibroblasts in pancreatic cancer*. *J Exp Med*, 2017. **214**(3): p. 579-596.
31. Helms, E., M.K. Onate, and M.H. Sherman, *Fibroblast Heterogeneity in the Pancreatic Tumor Microenvironment*. *Cancer Discov*, 2020. **10**(5): p. 648-656.
32. Hutton, C., et al., *Single-cell analysis defines a pancreatic fibroblast lineage that supports anti-tumor immunity*. *Cancer Cell*, 2021. **39**(9): p. 1227-1244.e20.
33. Elyada, E., et al., *Cross-Species Single-Cell Analysis of Pancreatic Ductal Adenocarcinoma Reveals Antigen-Presenting Cancer-Associated Fibroblasts*. *Cancer Discov*, 2019. **9**(8): p. 1102-1123.
34. Mollica, H., et al., *A 3D pancreatic tumor model to study T cell infiltration*. *Biomater Sci*, 2021. **9**(22): p. 7420-7431.
35. Nagl, L., et al., *Tumor Endothelial Cells (TECs) as Potential Immune Directors of the Tumor Microenvironment - New Findings and Future Perspectives*. *Front Cell Dev Biol*, 2020. **8**: p. 766.
36. Santos, C.R. and A. Schulze, *Lipid metabolism in cancer*. *Febs j*, 2012. **279**(15): p. 2610-23.
37. Cai, Z., et al., *Cancer-associated adipocytes exhibit distinct phenotypes and facilitate tumor progression in pancreatic cancer*. *Oncol Rep*, 2019. **42**(6): p. 2537-2549.
38. Incio, J., et al., *Obesity-Induced Inflammation and Desmoplasia Promote Pancreatic Cancer Progression and Resistance to Chemotherapy*. *Cancer Discov*, 2016. **6**(8): p. 852-69.
39. Meyer, K.A., et al., *Adipocytes promote pancreatic cancer cell proliferation via glutamine transfer*. *Biochem Biophys Res*, 2016. **7**: p. 144-149.
40. Cavel, O., et al., *Endoneurial macrophages induce perineural invasion of pancreatic cancer cells by secretion of GDNF and activation of RET tyrosine kinase receptor*. *Cancer Res*, 2012. **72**(22): p. 5733-43.
41. Bakst, R.L., et al., *Inflammatory Monocytes Promote Perineural Invasion via CCL2-Mediated Recruitment and Cathepsin B Expression*. *Cancer Res*, 2017. **77**(22): p. 6400-6414.

42. Kamiya, A., et al., *Genetic manipulation of autonomic nerve fiber innervation and activity and its effect on breast cancer progression*. Nat Neurosci, 2019. **22**(8): p. 1289-1305.
43. Ager, C.R., et al., *High potency STING agonists engage unique myeloid pathways to reverse pancreatic cancer immune privilege*. J Immunother Cancer, 2021. **9**(8).
44. Corrales, L., et al., *Direct Activation of STING in the Tumor Microenvironment Leads to Potent and Systemic Tumor Regression and Immunity*. Cell Rep, 2015. **11**(7): p. 1018-30.
45. Jing, W., et al., *STING agonist inflames the pancreatic cancer immune microenvironment and reduces tumor burden in mouse models*. J Immunother Cancer, 2019. **7**(1): p. 115.
46. Cheng, H., et al., *Activation of STING by cGAMP Regulates MDSCs to Suppress Tumor Metastasis via Reversing Epithelial-Mesenchymal Transition*. Front Oncol, 2020. **10**: p. 896.
47. Liang, H., et al., *Host STING-dependent MDSC mobilization drives extrinsic radiation resistance*. Nat Commun, 2017. **8**(1): p. 1736.
48. Swann, J.B., et al., *Type I IFN contributes to NK cell homeostasis, activation, and antitumor function*. J Immunol, 2007. **178**(12): p. 7540-9.
49. Nicolai, C.J., et al., *NK cells mediate clearance of CD8(+) T cell-resistant tumors in response to STING agonists*. Sci Immunol, 2020. **5**(45).
50. Su, T., et al., *STING activation in cancer immunotherapy*. Theranostics, 2019. **9**(25): p. 7759-7771.
51. Rosewell Shaw, A., et al., *Oncolytic adeno-immunotherapy modulates the immune system enabling CAR T-cells to cure pancreatic tumors*. Commun Biol, 2021. **4**(1): p. 368.
52. Müller, L., P. Aigner, and D. Stoiber, *Type I Interferons and Natural Killer Cell Regulation in Cancer*. Front Immunol, 2017. **8**: p. 304.
53. Gulen, M.F., et al., *Signalling strength determines proapoptotic functions of STING*. Nat Commun, 2017. **8**(1): p. 427.
54. Cerboni, S., et al., *Intrinsic antiproliferative activity of the innate sensor STING in T lymphocytes*. J Exp Med, 2017. **214**(6): p. 1769-1785.
55. Patel, S., et al., *The Common R71H-G230A-R293Q Human TMEM173 Is a Null Allele*. J Immunol, 2017. **198**(2): p. 776-787.
56. Gonugunta, V.K., et al., *Trafficking-Mediated STING Degradation Requires Sorting to Acidified Endolysosomes and Can Be Targeted to Enhance Anti-tumor Response*. Cell Rep, 2017. **21**(11): p. 3234-3242.
57. Tang, C.H., et al., *Agonist-Mediated Activation of STING Induces Apoptosis in Malignant B Cells*. Cancer Res, 2016. **76**(8): p. 2137-52.
58. Walker, M.M., et al., *B Cell-Intrinsic STING Signaling Triggers Cell Activation, Synergizes with B Cell Receptor Signals, and Promotes Antibody Responses*. J Immunol, 2018. **201**(9): p. 2641-2653.
59. Braun, D., I. Caramalho, and J. Demengeot, *IFN-alpha/beta enhances BCR-dependent B cell responses*. Int Immunol, 2002. **14**(4): p. 411-9.
60. Arwert, E.N., et al., *STING and IRF3 in stromal fibroblasts enable sensing of genomic stress in cancer cells to undermine oncolytic viral therapy*. Nat Cell Biol, 2020. **22**(7): p. 758-766.
61. Demaria, O., et al., *STING activation of tumor endothelial cells initiates spontaneous and therapeutic antitumor immunity*. Proc Natl Acad Sci U S A, 2015. **112**(50): p. 15408-13.
62. Yang, H., et al., *STING activation reprograms tumor vasculatures and synergizes with VEGFR2 blockade*. J Clin Invest, 2019. **129**(10): p. 4350-4364.
63. Buchanan, C.M., et al., *DMXAA (Vadimezan, ASA404) is a multi-kinase inhibitor targeting VEGFR2 in particular*. Clin Sci (Lond), 2012. **122**(10): p. 449-57.
64. Bai, J., et al., *DsbA-L prevents obesity-induced inflammation and insulin resistance by suppressing the mtDNA release-activated cGAS-cGAMP-STING pathway*. Proc Natl Acad Sci U S A, 2017. **114**(46): p. 12196-12201.
65. Vila, I.K., et al., *STING orchestrates the crosstalk between polyunsaturated fatty acid metabolism and inflammatory responses*. Cell Metab, 2022. **34**(1): p. 125-139.e8.
66. Akhmetova, K., M. Balasov, and I. Chesnokov, *Drosophila STING protein has a role in lipid metabolism*. Elife, 2021. **10**.
67. Xia, T., et al., *Deregulation of STING Signaling in Colorectal Carcinoma Constrains DNA Damage Responses and Correlates With Tumorigenesis*. Cell Rep, 2016. **14**(2): p. 282-97.
68. Vriens, K., et al., *Evidence for an alternative fatty acid desaturation pathway increasing cancer plasticity*. Nature, 2019. **566**(7744): p. 403-406.

69. Zhu, Z., et al., *Nerve growth factor expression correlates with perineural invasion and pain in human pancreatic cancer*. J Clin Oncol, 1999. **17**(8): p. 2419-28.
70. Donnelly, C.R., et al., *STING controls nociception via type I interferon signalling in sensory neurons*. Nature, 2021. **591**(7849): p. 275-280.
71. Chen, Q., et al., *Carcinoma-astrocyte gap junctions promote brain metastasis by cGAMP transfer*. Nature, 2016. **533**(7604): p. 493-498.
72. Motedayen Aval, L., et al., *Challenges and Opportunities in the Clinical Development of STING Agonists for Cancer Immunotherapy*. J Clin Med, 2020. **9**(10).
73. Amin, S., et al., *The impact of immunotherapy on the survival of pancreatic adenocarcinoma patients who received definitive surgery of the pancreatic tumor: a retrospective analysis of the National Cancer Database*. Radiat Oncol, 2020. **15**(1): p. 139.
74. Torchilin, V.P., *Recent approaches to intracellular delivery of drugs and DNA and organelle targeting*. Annu Rev Biomed Eng, 2006. **8**: p. 343-75.
75. Li, L., et al., *Hydrolysis of 2'3'-cGAMP by ENPP1 and design of nonhydrolyzable analogs*. Nat Chem Biol, 2014. **10**(12): p. 1043-8.
76. Nakamura, T., et al., *Liposomes loaded with a STING pathway ligand, cyclic di-GMP, enhance cancer immunotherapy against metastatic melanoma*. J Control Release, 2015. **216**: p. 149-57.
77. Leach, D.G., et al., *STINGel: Controlled release of a cyclic dinucleotide for enhanced cancer immunotherapy*. Biomaterials, 2018. **163**: p. 67-75.
78. Lu, X., et al., *Engineered PLGA microparticles for long-term, pulsatile release of STING agonist for cancer immunotherapy*. Sci Transl Med, 2020. **12**(556).
79. Kim, D.S., et al., *E7766, a Macrocyclic-Bridged Stimulator of Interferon Genes (STING) Agonist with Potent Pan-Genotypic Activity*. ChemMedChem, 2021. **16**(11): p. 1740-1743.
80. Liu, K., et al., *Development of small molecule inhibitors/agonists targeting STING for disease*. Biomed Pharmacother, 2020. **132**: p. 110945.
81. Le Naour, J., et al., *Trial watch: STING agonists in cancer therapy*. Oncoimmunology, 2020. **9**(1): p. 1777624.
82. Conlon, J., et al., *Mouse, but not human STING, binds and signals in response to the vascular disrupting agent 5,6-dimethylxanthenone-4-acetic acid*. J Immunol, 2013. **190**(10): p. 5216-25.
83. Shih, A.Y., K.L. Damm-Ganamet, and T. Mirzadegan, *Dynamic Structural Differences between Human and Mouse STING Lead to Differing Sensitivity to DMXAA*. Biophys J, 2018. **114**(1): p. 32-39.
84. Nakamura, T., et al., *STING agonist loaded lipid nanoparticles overcome anti-PD-1 resistance in melanoma lung metastasis via NK cell activation*. J Immunother Cancer, 2021. **9**(7).
85. Kinkead, H.L., et al., *Combining STING-based neoantigen-targeted vaccine with checkpoint modulators enhances antitumor immunity in murine pancreatic cancer*. JCI Insight, 2018. **3**(20).
86. Smith, T.T., et al., *Biopolymers codelivering engineered T cells and STING agonists can eliminate heterogeneous tumors*. J Clin Invest, 2017. **127**(6): p. 2176-2191.
87. Baird, J.R., et al., *Radiotherapy Combined with Novel STING-Targeting Oligonucleotides Results in Regression of Established Tumors*. Cancer Res, 2016. **76**(1): p. 50-61.
88. Taffoni, C., et al., *Nucleic Acid Immunity and DNA Damage Response: New Friends and Old Foes*. Front Immunol, 2021. **12**: p. 660560.
89. Cheradame, L., et al., *STING protects breast cancer cells from intrinsic and genotoxic-induced DNA instability via a non-canonical, cell-autonomous pathway*. Oncogene, 2021. **40**(49): p. 6627-6640.
90. Ahn, J., et al., *Inflammation-driven carcinogenesis is mediated through STING*. Nat Commun, 2014. **5**: p. 5166.
91. Thomsen, M.K., et al., *Lack of immunological DNA sensing in hepatocytes facilitates hepatitis B virus infection*. Hepatology, 2016. **64**(3): p. 746-59.